International Journal of Diabetes and Endocrinology
2022; 7(2): 22-28
http://www.sciencepublishinggroup.com/j/ijde
doi: 10.11648/j.ijde.20220702.11
ISSN: 2640-1363 (Print); ISSN: 2640-1371 (Online)

Review Article

Changing Era of Diabetes Management – A New Perspective for Dapagliflozin

Manish Maladkar*, Ashok Yadav, Shraddha Ghorui

Scientific Department, Aristo Pharmaceuticals Private Ltd., Mumbai, India

Email address:

scientific@aristopharma.co.in (M. Maladkar), ashok.yadav@aristopharma.co.in (A. Yadav), shraddha.ghorui@aristopharma.co.in (S. Ghorui)

*Corresponding author

To cite this article:

Manish Maladkar, Ashok Yadav, Shraddha Ghorui. Changing Era of Diabetes Management – A New Perspective for Dapagliflozin. *International Journal of Diabetes and Endocrinology*. Vol. 7, No. 2, 2022, pp. 22-28. doi: 10.11648/j.ijde.20220702.11

Received: February 21, 2022; **Accepted**: March 26, 2022; **Published**: April 9, 2022

Abstract: Type 2 Diabetes Mellitus (T2DM) treatment has progressed dramatically in recent decades. The recent major expansion of the evidence base for T2DM treatment has resulted in frequent revisions of guidelines for hyperglycemia management. When there were few pharmaceutical options, the management strategy was glucocentric or hyperglycemic control. There has been a significant change from the glucocentric era to a more patient-centered and organ-protection era evident in clinical practice guidelines of diabetes management. In addition, since the diabetes armamentarium has grown and new information has been available, the focus has shifted from hyperglycemia control to a more holistic approach, including cardiovascular and renal benefits of the drugs and safety concerns such as weight gain, hypoglycemia. The introduction of the Sodium-Glucose Cotransporter 2 (SGLT2) inhibitor class of medications has had a substantial impact on diabetes management. The constant positive findings of multiple Cardiovascular Outcome Trials (CVOTs) with SGLT2 inhibitors prompted a paradigm shift: from hyperglycemia control to a patient-centered approach. As a result, SGLT2 inhibitors have been identified by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) as an ideal class for a more patient-centered approach to T2DM treatment, become a driving force in diabetes care. Dapagliflozin, an SGLT2 inhibitor, has recently emerged as a glucose-lowering medication that has been found to not only be successful in lowering glycemic levels but also to improve cardio-renal outcomes in diabetic patients. Furthermore, Dapagliflozin is the first anti-diabetic drug to show cardiac and renal benefits even in those who do not have diabetes. As a result, Dapagliflozin has paved the way for a future organ protection strategy for diabetes as well as non-diabetes.

Keywords: Dapagliflozin, Type 2 Diabetes, SGLT2 Inhibitors, DAPA-HF, DAPA-CKD, Heart Failure, CKD

1. Introduction

Diabetes is a serious health problem that has reached epidemic proportions. According to the International Diabetes Federation (IDF), the number of diabetics worldwide is expected to climb dramatically by 2045. Diabetes currently affects 537 million people around the world. [1] Diabetes patients have a higher risk of long-term consequences, including increased morbidity and mortality. Atherosclerotic cardiovascular disease (ASCVD), which includes myocardial infarction (MI), unstable angina, stroke, and peripheral arterial disease, affects nearly one-third of patients with T2DM. Diabetes increases the risk of various microvascular issues, including eye, nerve, and foot problems. Diabetic kidney disease affects over 40% of diabetic individuals and is the most common cause of Chronic Kidney Disease (CKD) worldwide. [2] As our knowledge of diabetes and its complications has evolved, so has our understanding of different targets and the development of treatment options. This review article aims to summarize the progress in understanding of disease pathogenesis and changing approaches in the management of T2DM over the course of time. We have classified the progress of T2DM management into three eras based on the available agents, clinical evidence, therapeutic strategies, and guideline recommendations. Our recent data-driven literature search

highlights the role of Dapagliflozin in diabetes management and its relevance across all eras.

2. The Diabetes Knowledge Explosion

2.1. Pathogenesis of T2DM: From the Triumvirate to the Ominous Octet & the Faithless Fourteen

The way we address and manage the condition has improved as our understanding of pathogenesis has progressed. Diabetes has progressed from being regarded to be disease of insulin deficiency to one characterized by insulin resistance (mediated by the liver, muscle, and fat cells) and deficiency, resulting in the multidimensional syndrome we know today.

Dr. DeFronzo developed the concept of insulin resistance, the defining characteristic of T2DM, resulting in novel ideas about the development and progression of diabetes. According to him, the primary pathophysiology of type 2 diabetes included three abnormalities known as the triumvirate, which led to more findings and brought other organ- systems to center stage. The term ominous octet was hence proposed. [3] Later, six more factors were added to the pathogenic mechanisms, taking the number of defects in diabetes up to 14 (Faithless Fourteen). [4]

2.2. The Triumvirate

Insulin resistance, pancreatic β-cell dysfunction, and increased hepatic glucose output were the traditional pathophysiological defects of T2DM. Insulin resistance is the first detectable abnormality in people who are pre-diabetic. It can begin years, if not decades before a diabetes diagnosis is made. As a person develops diabetes, the mass of β-cells decreases, contributing to decreased insulin secretion.

Under fasting conditions, the liver contributes to the maintenance of normoglycemia through gluconeogenesis and glycogenolysis. Insulin inhibits both gluconeogenesis and glycogenolysis. As a result, insulin resistance in the liver leads to increased hepatic glucose output. [3]

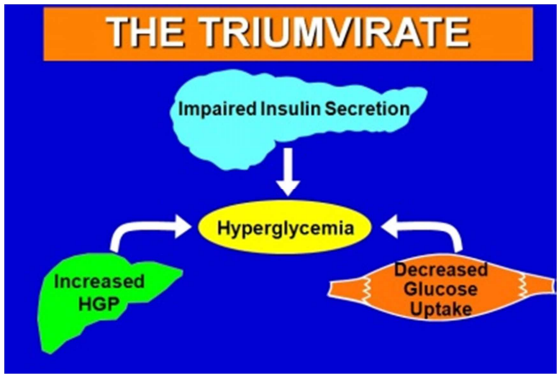

Figure 1. *The triumvirate.*

2.3. The Ominous Octet

In addition to the known factors, multiple defects involving multiple organ systems contributing to the progression of hyperglycemia in T2DM were also discovered. Adipocytes (accelerated lipolysis), the gastrointestinal tract (incretin deficiency/resistance), pancreatic α-cells (hyperglucagonemia), the brain (neurotransmitter dysfunction), and the kidneys (increased glucose reabsorption) are among those affected. [3]

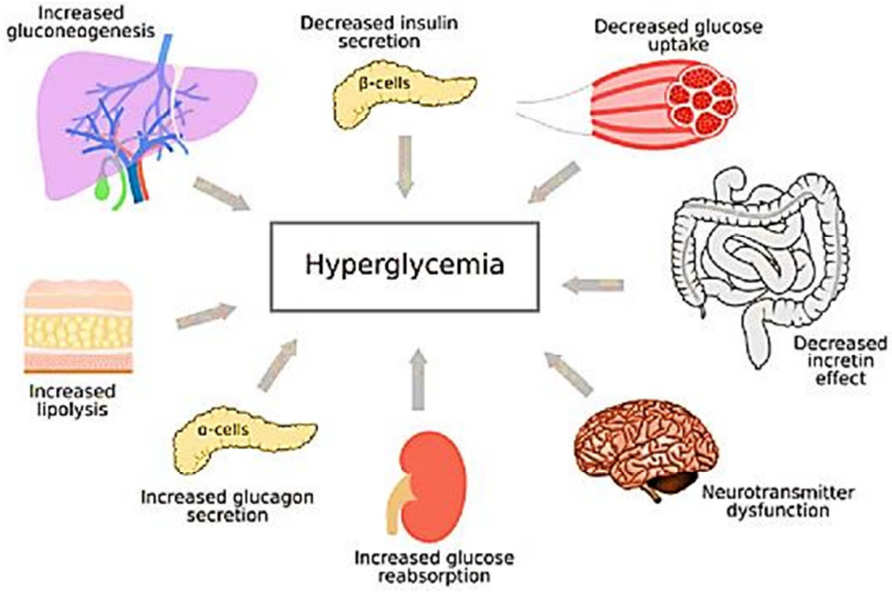

Figure 2. *The Ominous Octet.*

2.4. The Faithless Fourteen

However, diabetes has a lot more in store for us. Reduced dopamine levels, vitamin D deficiency, gut-derived serotonin, testosterone deficit, renin-angiotensin system, and iron overload *(The Faithless Fourteen)* have all been linked to worsening of hyperglycemia in diabetes patients. [4]

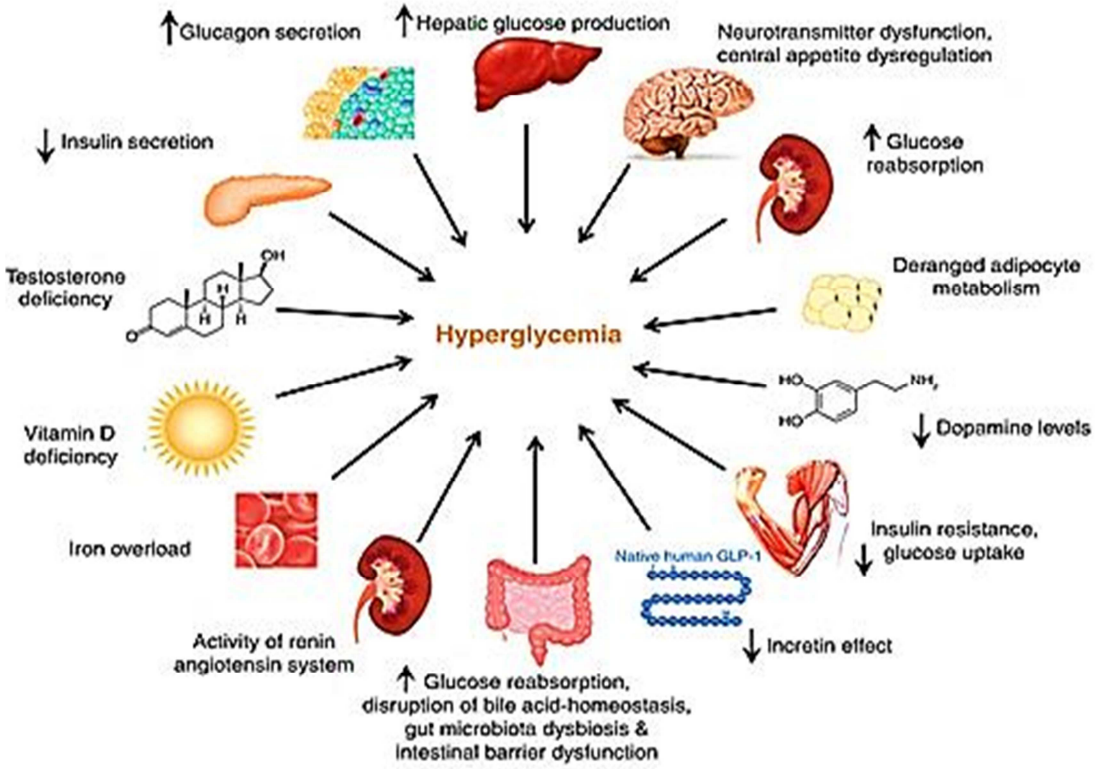

Figure 3. *The Faithless Fourteen.*

3. Therapeutic Options: From Then to Now and Beyond

T2DM management has progressed from a glucocentric to an organ-protective approach in recent years. In addition, as our understanding of the underlying pathophysiological abnormalities has advanced, the number of therapeutic options for T2DM has grown, resulting in periodic changes to clinical practice guidelines for managing T2DM. On the basis of therapeutic strategy, the management of T2DM may be split into three eras:

i. Glucocentric era
ii. Patient-centered era
iii. Organ-protection era

3.1. Glucocentric Era

T2DM has traditionally been managed by focusing on hyperglycemia control, primarily measured by glycated hemoglobin (HbA1c). Insulin, sulfonylureas, biguanides, thiazolidinediones, and alpha-glucosidase inhibitors were the only glucose-lowering drugs available. As a result, T2DM management centered solely on hyperglycemia control. During this time, the goal of treatment was to get HbA1c as close to normal as feasible. Furthermore, as the diabetic arsenal had grown and other evidences from studies like ACCORD *(Action to Control Cardiovascular Risk in Diabetes)* [5], ADVANCE *(Action in Diabetes and Vascular Disease: Preterax and Diamicron Modifed Release Controlled Evaluation)* [6], and VADT *(Veterans Affairs Diabetes Trial)* [7] became accessible, the focus shifted to include not just HbA1c control but also safety concerns such as weight gain and hypoglycemia while considering T2DM management. [8]

3.2. Patient-Centric Era

With the expanding therapy choices for T2DM, clinicians now focus on a patient-centered approach to target particular underlying pathophysiological problems associated with the condition. Other than HbA1c, a variety of parameters are taken into account. Disease states, co-morbidities such as the existence of high risk of ASCVD, CKD, and Heart Failure (HF), drug efficacy and safety profiles, patient preference, and cost are now all taken into account alongside HbA1c when developing the best diabetes care strategy for each patient.

Multiple agents from 12 distinct pharmacological classes are now part of the ever-expanding treatment arsenal. Notably, the introduction of the SGLT2 inhibitors class of medications has shaped and evolved diabetes care dramatically. The positive outcomes of numerous CVOTs using SGLT2 Inhibitors prompted a paradigm shift: from a glucocentric to a patient-centric strategy.

The results of these CVOTs have been incorporated into treatment recommendations by several scientific societies, including the ADA, American Association of Clinical Endocrinology (AACE), American College of Cardiology (ACC), and others. Accordingly, the findings including cardiovascular (CV) complications reduction in T2DM patients are upgraded in expert guidelines. [9]

3.3. Organ-Protection Era

It must be recognized that in this new era, treatment has progressed beyond just addressing risk factors to selecting the most effective cardio- or renoprotective medicine as an individualized therapy in order to reduce CV events. It represents a significant paradigm shift where both hyperglycemia and other risk factors are given equal attention while managing diabetes.

The cardiorenal advantages of SGLT-2 inhibitors' have been confirmed in individuals with heart failure and/or renal impairment without diabetes. Utilization of these drugs for their CV and renoprotective properties, irrespective of diabetes status may be the start of a new era. [10]

4. SGLT2 Inhibitors for the Management of T2DM

The SGLT2 Inhibitors are a class of anti-diabetic drugs which, due to their multiple pleiotropic benefits play a critical role in the overall management of diabetic patients. They interfere in the metabolic pathway while having no effect on β-cell function or insulin resistance. SGLT2 inhibitors have proven to reduce the risk of macrovascular and microvascular complications by providing glycemic control, significant body weight loss, and reduction in blood pressure. Furthermore, prevention of diabetes complications and improvement in quality of life is inevitable with a patient-centered approach and individualized treatment option with SGLT2 inhibitor medication. [11]

The SGLT2 inhibitors including Dapagliflozin, Canagliflozin, Empagliflozin, and, most recently, Ertugliflozin are approved by the European Medicines Agency (EMA) and the Food and Drug Administration (USFDA) as monotherapy or as an add-on to other antidiabetic drugs. Only Japan has approved Ipragliflozin, Luseogliflozin, and Tofogliflozin. Remogliflozin is another SGLT2 inhibitor commercially available in India. [12]

4.1. Mechanism of Action

SGLT2 inhibitors act through kidney to manage the glucose metabolism and homeostasis. Kidney plays an important role in glucose homeostasis through renal gluconeogenesis, glomerular filtration, and glucose reabsorption in the proximal convoluted tubule (PCT). The kidney can filter roughly 180 g of glucose per day in a healthy person and all of this filtered glucose is reabsorbed back into the circulation through PCT. The SGLT receptor family (6 members, SGLT 1–6) is responsible for this glucose reabsorption mechanism in the PCT. The SGLT2 receptor is present in the S1 segment of the PCT; whereas the SGLT1 receptor is found in the S2/S3 region. Approximately 90% reabsorption of glucose takes place in the S1 segment, while ~ 10% gets reabsorbed in the S2/S3 segments of the PCT). A passive transport mechanism involving facilitative glucose transporters returns all of the reabsorbed glucose to circulation. SGLT2 expression is upregulated in diabetic patients which leads to an increase in the renal threshold as a result, increasing the blood glucose level. [13]

The SGLT2 inhibitor selectively inhibits the SGLT2 receptors and reduces glucose reabsorption in the PCT, causing increased urinary glucose excretion (UGE) and thus lowering hyperglycemia. Furthermore, SGLT2 inhibitors therapy causes persistent calorie loss leading to weight reduction, reduction in β-cell stress & hyperinsulinemia, increased insulin sensitivity & rate of insulin secretion. Regardless of insulin resistance or β-cell dysfunction, all of these mechanisms regulate blood glucose level. Furthermore, because of their insulin-independent mechanism of action, SGLT2 inhibitors may be helpful in advanced stages of T2DM (when pancreatic β-cell reserves are permanently lost). [13]

SGLT2 inhibitors have created a significant place in the T2DM management. They have some distinct advantages of weight and BP reduction, low risk of hypoglycemia, and reduction in macrovascular and microvascular events. Furthermore, these medications may also address some core defects in T2DM patients, such as improvement in β-cell function and insulin sensitivity. SGLT2 inhibitors have been recommended as monotherapy and combination therapy in the treatment of T2DM by different guidelines due to their numerous potential benefits. [13]

4.2. Dapagliflozin: Leading the Change in Patient– Centric Era

A recent CVOT with Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) [14] has given a new dimension to the diabetes clinical practice. Along with cardiovascular safety this trial also emphasizes the potential life- and organ-saving benefits of Dapagliflozin. Although ADA and AACE/ACE guidelines continues to prefer metformin as initial glucose-lowering pharmacotherapy in T2DM, they also recommends SGLT2 inhibitors to be considered as add-on therapies in patients with or at high risk for ASCVD, CKD, HF or heart failure with reduced ejection fraction (HFrEF) with or without diabetes. [15, 16]

DECLARE-TIMI 58 was a randomized controlled trial that looked at the cardiovascular safety of Dapagliflozin in T2DM. A total of 17,160 patients with T2DM were recruited either with developed ASCVD (40.6%) or ASCVD risk factors (59.4%). The follow up period was 4.2 years. The Dapagliflozin group had lower HbA1c throughout the trial as compared to placebo group. There was a significant metabolic benefit observed in terms of weight reduction (1.8 kg, 95% CI 1.7–2.0), and both systolic and diastolic blood pressure reduction (2.7 mmHg, 95% CI 2.4–3; 0.7 mmHg, 95% CI 0.6–0.9, respectively). Dapagliflozin treatment significantly reduced composite outcome [major adverse cardiac event (MACE) – including CV death, MI and ischemic stroke, CV death and hospitalization for heart failure (HHF)] by 17% (hazard ratio HR- 0.83; 4.9% vs. 5.8%). [14]

Dapagliflozin has shown significant benefits in Indian patients. Vishwanath V et al., conducted a real world

evidence study of Dapagliflozin (FOREFRONT) which included a total 1941 T2DM Indian patients to determine effectiveness of Dapagliflozin in the real-world setup. A retrospective and prospective data collection was done for 3 months. Primary endpoint (mean HbA1c) decreased significantly from baseline to month 3 by 1.00% and month 6 by 1.49%, P < 0.001. Decrease in mean body weight was significant from baseline to month 3 (1.14 kg) and month 6 (1.86 kg), P < 0.001. Maximum weight loss were seen in patients with BMI >30 kg/m^2 (1.60 kg and 2.56 kg) at months 3 and 6, respectively. There was also improvement in systolic/diastolic blood pressure. Findings from the study concluded that Dapagliflozin significantly decreases HbA1c and body weight in Indian T2DM patients without any major safety concerns. [17]

4.3. Dapagliflozin: Leading the Change in Organ-Protection Era

Dapagliflozin is the first anti-diabetic agent that has shown cardiac & renal beneficial effects even in subjects without diabetes. Two Trials – DAPA-HF *(Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure)* [18] & DAPA-CKD *(Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease)* [19] have confirmed the cardiac & renal beneficial effects even in subjects without diabetes. Dapagliflozin is being extensively used for its cardiovascular and renoprotective effects regardless of the presence or absence of diabetes. The DAPA-HF trial was conducted to see how Dapagliflozin affects individuals with HF with or without T2DM. A total 4744 patients with New York Heart Association (NYHA) class II, III, or IV HF and an ejection fraction of less than 40%. (i.e. HFrEF) were randomized to receive either Dapagliflozin 10 mg once day (OD) or a placebo on the background of standard therapy. T2DM patients continued to receive their usual antidiabetic medications. The incidence of composite primary outcome (HHF, urgent treatment for HF with IV medication, and CV death) was significantly lower by 30% in Dapagliflozin group as compared to placebo (HR 0.70, 95% CI 0.65–0.85, P< 0.001). The first episode of worsening HF (hospitalization or urgent visit resulting in intravenous therapy for HF) was significantly lower by 30% in Dapagliflozin group as compared to placebo group (HR 0.70, 95% CI 0.59–0.83). CV death and all-cause death were significantly lower by 18% (HR 0.82, 95% CI 0.71–0.97) & 17% (HR, 0.83; 95% CI, 0.71 to 0.97) in Dapagliflozin group as compared to placebo, respectively. Findings from DAPA-HF backed up the conclusion that SGLT2 inhibitors can provide more mortality benefit in the patients with a greater degree of renal disease. [18]

The DAPA CKD trial evaluated the efficacy and safety of Dapagliflozin in CKD patients with and without a T2DM diagnosis. 4304 patients with an eGFR of 25–75 ml/min/1.73 m^2 and a urinary albumin–creatinine ratio (ACR) of 200–5000 mg/g were randomized to receive either Dapagliflozin 10 mg OD or placebo and followed for a median period of 2.4 years. Patients in the Dapagliflozin group showed a significant 44% lower risk of the composite outcome [*a ≥ 50% decline in eGFR seen ≥28 days; the onset of end-stage renal disease (defined as ≥28 days of dialysis, renal transplant, or eGFR <15 ml/min/1.73 m^2); death from any renal or CV cause]* as compared to placebo group (HR 0.56, 95% CI 0.45– 0.68, P < 0.001). Dapagliflozin group also showed a significant lower risk of CV death or HF and all-cause mortality by 29% (HR 0.71, 95% CI, 0.55–0.92; P = 0.009) & 31% (HR, 0.69; 95% CI, 0.53 - 0.88; P = 0.004), respectively. [19] Based on the findings from DAPA-CKD trial, both United States and European Union have approved the usage of Dapagliflozin in CKD patients irrespective of diabetes. [20, 21] Also, the Indian authority-Drug Controller General of India have approved Dapagliflozin for the treatment of patients of CKD up to Stage III (eGFR of ≥ 30ml/min/1.73m^2). [22]

4.4. Dapagliflozin: Quō vādis

In recent years, research on SGLT2 inhibitors has yielded highly encouraging results. The landmark trials like DECLARE TIMI-58, DAPA-HF, and DAPA-CKD have significantly changed the management of T2DM. Each study established the crucial role of Dapagliflozin in diabetes management and further expanded its indications beyond T2DM. The encouraging result from these studies has created a strong foundation for future clinical trials exploring different indications. DAPA-MI *(DAPAgliflozin effects in patients without diabetes with Myocardial Infarction)* [23] and DICTATE-AHF *(the efficacy and safety of DapaglIflozin in aCuTe heArT failurE trial)* [24] are two studies aimed to expand the usage of Dapagliflozin in myocardial infarction (MI) and acute HF patients, respectively. The DAPA-MI study will assess Dapagliflozin's use in acute MI population with an aim to reduce the risk of hospitalization for consequent HF. [23] The DICTATE-AHF trial will include T2DM patients hospitalized due to hypovolemic acute heart failure (AHF). [24]

MI is a prominent cause of morbidity and mortality around the world, and if Dapagliflozin proves its efficiency in reducing these outcomes, it will likely become much more widely used in coming years, helping patients with T2DM and acute MI. SGLT2 inhibitors may also form a cornerstone therapy in slowing the deteriorating renal function, in many CKD patients with or without diabetes. [25]

5. Conclusion

Normalizing HbA1c was the only focus in the glucocentric era. Further, with the availability of newer drugs, the focus has changed to control hyperglycemia but without any untoward adverse effects. Notably, the introduction of SGLT2 inhibitors class of drugs has significantly continued to shape & evolve diabetes management. Dapagliflozin has not only been shown to effectively control hyperglycemia but has proven to possess numerous extra glycemic benefits like cardio - renal - metabolic benefits. These benefits have altogether given rise to a new era where the focus has now changed from (only)

control of HbA1c to the patient-centric approach. Moreover, recent evidence with Dapagliflozin demonstrating cardio-renal benefits in patients even without diabetes is all set to create a future roadmap. Dapagliflozin is now used extensively for its cardiovascular and renoprotective effects regardless of the presence or absence of diabetes. On the basis of all these benefits, we can say Dapagliflozin is definitely leading the change in the management of T2DM. Dapagliflozin has expanded its indication from an oral antihyperglycemic agent to a therapy for Heart Failure & CKD. The prescription should be based on careful medical evaluation and a shared decision between the patient and the clinician backed by guideline recommendations.

Source(s) of Support

Aristo Pharmaceuticals Private Limited. Mumbai.

References

[1] International Diabetes Federation (IDF) Diabetes Atlas. 10th Edition (2021). Adapted from https://diabetesatlas.org/atlas/tenth-edition/ as accessed on 18 Feb 2021.

[2] Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clin J Am Soc Nephrol. 2017; 12 (12): 2032-2045. doi: 10.2215/CJN.11491116.

[3] Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009; 58 (4): 773-795. doi: 10.2337/db09-9028.

[4] Kalra S. Recent advances in pathophysiology of diabetes: beyond the dirty dozen. J Pak Med Assoc. 2013 Feb; 63 (2): 277-80.

[5] Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, et al. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008; 358 (24): 2545-59. doi: 10.1056/NEJMoa0802743.

[6] Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008; 358 (24): 2560-72. doi: 10.1056/NEJMoa0802987.

[7] Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009; 360 (2): 129-39. doi: 10.1056/NEJMoa0808431.

[8] Harris SB, Cheng AYY, Davies MJ, Gerstein HC, Green JB, Skolnik N. Person-Centered, Outcomes-Driven Treatment: A New Paradigm for Type 2 Diabetes in Primary Care. Arlington (VA): American Diabetes Association; 2020 May.

[9] Lahiri SW. Personalizing Type 2 Diabetes Management: Use of a Patient-Centered Approach to Individualizing A1C Goals and Pharmacological Regimens. Clin Diabetes. 2017; 35 (5): 321-328. doi: 10.2337/cd17-0083.

[10] Jacob S, Krentz AJ, Deanfield J, Rydén L. Evolution of Type 2 Diabetes Management from a Glucocentric Approach to Cardio-Renal Risk Reduction: The New Paradigm of Care. Drugs. 2021; 81 (12): 1373-1379. doi: 10.1007/s40265-021-01554-6.

[11] Dhillon S. Dapagliflozin: A Review in Type 2 Diabetes. Drugs. 2019; 79 (18): 2013. doi: 10.1007/s40265-019-01239-1.

[12] D. J. Wexler. Sodium-glucose co-transporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus. UpToDate, pp. 1–29, 2020, [Online]. Available: https://www.uptodate.com/contents/sodium-glucose-co-transporter-2-inhibitors-for-the-treatment-of-hyperglycemia-in-type-2-diabetes-mellitus?source=history_widget. as accessed on 18 Feb 2022.

[13] Singh AK, Unnikrishnan AG, Zargar AH, Kumar A, Das AK, Saboo B, et al. Evidence-Based Consensus on Positioning of SGLT2i in Type 2 Diabetes Mellitus in Indians. Diabetes Ther. 2019; 10 (2): 393-428. doi: 10.1007/s13300-019-0562-1.

[14] Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. DECLARE–TIMI 58 Investigators. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019; 380 (4): 347-357. doi: 10.1056/NEJMoa1812389.

[15] Garber AJ, Handelsman Y, Grunberger G, Einhorn D, Abrahamson MJ, Barzilay JI, et al. Consensus Statement By The American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Comprehensive Type 2 Diabetes Management Algorithm - 2020 Executive Summary. Endocr Pract. 2020; 26 (1): 107-139. doi: 10.4158/CS-2019-0472.

[16] Draznin B, Aroda VR, Bakris G, Benson G, Brown FM, Freeman R, et al. American Diabetes Association Professional Practice Committee; American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022; 45 (Supplement_1): S125-S143. doi: 10.2337/dc22-S009.

[17] Viswanathan V, Singh KP. Use of Dapagliflozin in the Management of Type 2 Diabetes Mellitus: A Real-World Evidence Study in Indian Patients (FOREFRONT). Diabetes Technol Ther. 2019; 21 (8): 415-422. doi: 10.1089/dia.2019.0052.

[18] McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019; 381 (21): 1995-2008. doi: 10.1056/NEJMoa1911303.

[19] Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020; 383 (15): 1436-1446. doi: 10.1056/NEJMoa2024816.

[20] FARXIGA-dapagliflozin tablet- Full Prescribing Information. Adapted from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=72ad22ae-efe6-4cd6-a302-98aaee423d69 as accessed on 18 Feb 2022.

[21] Forxiga- dapagliflozin tablet- Summary of Product Characteristics. Adapted from https://www.medicines.org.uk/emc/product/7607/smpc as accessed on 18 Feb 2022.

[22] Recommendations of the SEC (Cardiovascular & Renal). Adapted from https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadCommitteeFiles/Recommendation of SEC (Cardio & renal) 07.01.2021 & 08.01.2021.pdf. as accessed on 18 Feb 2022.

[23] ClinicalTrials.gov. Dapagliflozin Effects on Cardiovascular Events in Patients With an Acute Heart Attack (DAPA-MI) Adapted from https://clinicaltrials.gov/ct2/show/NCT04564742 as accessed on 18 Feb 2022.

[24] ClinicalTrials.gov. Efficacy and Safety of Dapagliflozin in Acute Heart Failure (DICTATE-AHF) Adapted from https://clinicaltrials.gov/ct2/show/NCT04298229 as accessed on 18 Feb 2022.

[25] Nicholson MK, Ghazal Asswad R, Wilding JP. Dapagliflozin for the treatment of type 2 diabetes mellitus - an update. Expert Opin Pharmacother. 2021; 22 (17): 2303-2310. doi: 10.1080/14656566.2021.1953471.